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Review

Belantamab Mafodotin in Multiple Myeloma: Molecular Mechanisms, Immunobiology, Resistance, and Clinical Repositioning

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Abstract

Belantamab mafodotin, a B-cell maturation antigen (BCMA)-targeted antibody–drug conjugate (ADC), has emerged as an important therapeutic option in the evolving treatment landscape of multiple myeloma (MM). Its clinical development has progressed from single-agent activity in heavily pretreated patients to combination strategies demonstrating significant clinical benefit in relapsed/refractory disease. This narrative review provides an integrated overview of the molecular structure, mechanisms of action, immunobiological effects, resistance pathways, toxicity profile, and evolving clinical positioning of belantamab mafodotin. Preclinical studies support multiple complementary mechanisms, including direct cytotoxicity through intracellular delivery of monomethyl auristatin F (MMAF), antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and immunogenic cell death. The contribution of immunogenic cell death and other effects on the tumor microenvironment to clinical benefit remains unproven. Potential resistance mechanisms include alterations in BCMA expression, impaired intracellular processing, payload-related resistance, and changes in immune effector function. The characteristic ocular toxicity, particularly keratopathy, remains the principal treatment-limiting adverse effect and reflects, at least partly, BCMA-independent uptake of the ADC by corneal epithelial cells. Clinical evidence from the phase III DREAMM-7 and DREAMM-8 trials has established the efficacy of belantamab-containing combinations, with significant improvements in progression-free survival compared with their respective control regimens. In contrast, belantamab mafodotin monotherapy did not demonstrate superiority for the primary progression-free survival endpoint of DREAMM-3. Emerging combination strategies, including regimens incorporating immunomodulatory drugs, proteasome inhibitors, and γ-secretase inhibitors, may further expand its therapeutic applications. Meanwhile, the optimal sequencing of belantamab mafodotin with BCMA-directed chimeric antigen receptor T-cell therapies and bispecific antibodies remains unresolved. Overall, belantamab mafodotin represents an evolving BCMA-targeted treatment strategy in MM. Future research should focus on identifying predictive biomarkers, optimizing dosing schedules to minimize ocular toxicity, defining effective combination approaches, and establishing evidence-based sequencing strategies to maximize clinical benefit.

Keywords: belantamab mafodotin; multiple myeloma; B-cell maturation antigen (BCMA); antibody–drug conjugate; immunobiology; mechanisms of resistance; ocular toxicity; treatment sequencing; BCMA-targeted therapy

1. Introduction

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Multiple myeloma (MM) is a hematologic malignancy characterized by clonal plasma cell proliferation in the bone marrow. It accounts for approximately 1% of all cancers and about 10% of hematologic malignancies [1,2]. Proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) and anti-CD38 monoclonal antibodies have substantially prolonged survival. Nonetheless, the disease relapses in the large majority of patients; in MM refractory to all three drug classes (triple-class refractory), treatment options are limited and the prognosis is poor [1].

B-cell maturation antigen (BCMA) is among the best-characterized targets in the treatment of MM and is currently addressed through three therapeutic modalities: chimeric antigen receptor (CAR) T-cell therapies (idecabtagene vicleucel [ide-cel], ciltacabtagene autoleucel [cilta-cel]), T-cell–redirecting bispecific antibodies (e.g., teclistamab), and the antibody–drug conjugate (ADC) belantamab mafodotin [3–5]. As an off-the-shelf ADC, belantamab mafodotin avoids the patient-specific manufacturing interval required for autologous CAR-T-cell therapy, an availability advantage also shared by bispecific antibodies. Its safety profile differs from that of T-cell–redirecting therapies: ocular toxicity is a characteristic concern with belantamab, whereas cytokine release syndrome, neurotoxicity, cytopenias, infections, and hypogammaglobulinemia are relevant considerations with CAR-T-cell therapies and bispecific antibodies, with their frequency and severity varying by agent and regimen.

The clinical development of belantamab mafodotin began with the demonstration of single-agent activity in the first-in-human DREAMM-1 study [6,7]; in the phase II DREAMM-2 trial, response rates of approximately 31–34% were reported in triple-class-exposed patients [8]. The phase III DREAMM-7 and DREAMM-8 trials, which evaluated belantamab in combination with bortezomib–dexamethasone and pomalidomide–dexamethasone, respectively, were published in 2024 [9,10].

The factor that most shapes the clinical use of belantamab is its characteristic ocular toxicity (keratopathy) and the frequent dose modifications it necessitates [9,10]. Understanding the molecular architecture of the drug, its intracellular trafficking, and its cellular effects in both tumor and healthy tissues is therefore also clinically relevant. This narrative review integrates BCMA biology and ADC design with the mechanisms of belantamab mafodotin activity, resistance, and ocular toxicity. It critically examines candidate biomarkers and the clinical evidence supporting belantamab-containing combinations, distinguishing established findings from experimental observations and mechanistic hypotheses. The aim is to connect molecular understanding with patient selection, treatment optimization, and unresolved questions regarding therapeutic sequencing.

2. BCMA Biology and Its Role in Multiple Myeloma

BCMA (TNFRSF17/CD269) is a member of the tumor necrosis factor (TNF) receptor superfamily. It possesses a short extracellular region (a single cysteine-rich domain) and is structurally related to the B-cell activating factor receptor (BAFF-R) and transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) [11,12]. Its ligands are a proliferation-inducing ligand (APRIL; higher affinity) and B-cell activating factor (BAFF). Ligand binding activates canonical and non-canonical nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K)/AKT signaling through TNF receptor-associated factor (TRAF) adaptor proteins, thereby increasing the expression of antiapoptotic proteins such as Mcl-1, Bcl-2 and Bcl-xL and supporting cell survival [11–14].

Under physiological conditions, BCMA expression is restricted to late B-cell stages and plasma cells; it is not detected on naive B cells, hematopoietic stem cells, or non-hematopoietic tissues. Early studies implicated BCMA in the survival of long-lived bone marrow plasma cells [15]. However, a recent study using two independent BCMA-deficient mouse models found that long-lived antigen-specific plasma cells were maintained in the absence of BCMA, challenging the view that this receptor is universally required for plasma cell persistence [16]. The relevance of these findings to human plasma cell survival and malignant plasma cell biology remains to be established. In MM, BCMA is expressed at the cell surface in virtually all cases, although the density of expression is heterogeneous

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across patients [11,17,18]. The plasma cell–restricted expression pattern and frequent presence of BCMA on myeloma cells provide a biological rationale for therapeutic targeting. However, variability in surface antigen density means that widespread expression should not be equated with uniform susceptibility to BCMA-directed treatment [17,18].

The bone marrow microenvironment is the principal source of the ligands that drive BCMA signaling. BAFF and APRIL are produced by stromal cells, osteoclasts and myeloid cells, and protect MM cells from apoptosis induced by interleukin-6 deprivation and dexamethasone [13,14]. The APRIL–BCMA axis additionally contributes to the establishment of an immunosuppressive microenvironment [19]. BCMA is therefore not merely a surface marker but a functional component of the survival and immune-escape program of the tumor cell.

An important property of BCMA with respect to ADC therapy is γ-secretase-mediated shedding. γ-Secretase directly cleaves BCMA, releasing soluble BCMA (sBCMA), which acts as a decoy by binding APRIL. Conversely, γ-secretase inhibition increases surface BCMA expression [20]. Considered together with the demonstration that γ-secretase inhibitors enhance the efficacy of BCMA-directed CAR-T cells [21], this raises the prospect of combination strategies aimed at increasing target density (Figure 1). sBCMA is also a biomarker: it is elevated in MM and correlates with disease status and survival [22,23].

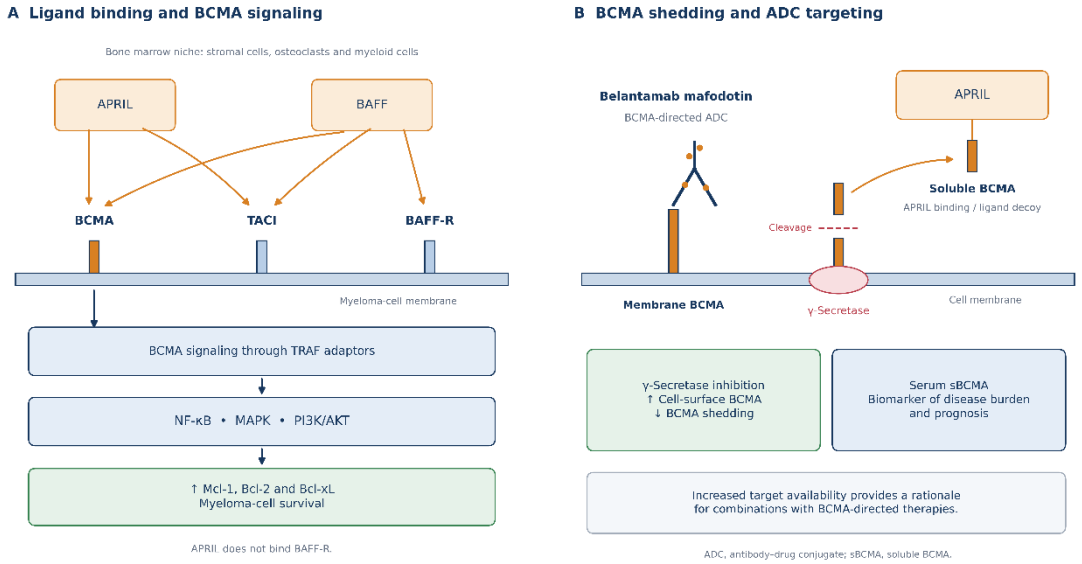

Figure 1. BCMA biology in the context of antibody–drug conjugate therapy. (A) APRIL binds BCMA and TACI, whereas BAFF binds BCMA, TACI and BAFF-R. APRIL and BAFF are supplied by cells within the bone marrow niche. BCMA-mediated signaling supports myeloma cell survival through pathways including NF-κB, MAPK and PI3K/AKT and the expression of antiapoptotic proteins such as Mcl-1, Bcl-2 and Bcl-xL. (B) γ-Secretase cleaves membrane-bound BCMA, releasing soluble BCMA (sBCMA), which can bind APRIL and serves as a biomarker of disease burden. γ-Secretase inhibition increases cell-surface BCMA availability, providing a rationale for combinations with BCMA-directed therapies. Belantamab mafodotin binds membrane-bound BCMA [11–23].

3. Antibody–Drug Conjugate Design of Belantamab Mafodotin

Belantamab mafodotin comprises an afucosylated, humanized IgG1 monoclonal antibody directed against BCMA, a protease-resistant, non-cleavable maleimidocaproyl (mc) linker, and the microtubule inhibitor monomethyl auristatin F (MMAF) as its payload [24]. Each component determines both efficacy and drug-specific toxicity [25,26] (Table 1).

Table 1. Components of belantamab mafodotin.

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Component	Property	Functional consequence
Antibody	Humanized IgG1 (J6M0; derived from the murine clone 118G03), high affinity for BCMA [24]	Selective binding; inhibition of ligand signaling
Fc	Afucosylated	Increased FcγRIIIa binding, enhanced antibody-dependent cellular cytotoxicity (ADCC) [24,27]
Linker	Maleimidocaproyl, non-cleavable, cysteine-linked	Stable in circulation; release requires lysosomal degradation of the antibody [28]
Payload	MMAF (an auristatin derived from dolastatin 10)	Inhibition of tubulin polymerization, G2/M arrest [24,28]
Active catabolite	cys-mcMMAF	Charged, poorly membrane-permeable; accumulates intracellularly [28,29]
DAR (drug-to-antibody ratio)	Approximately 4 on average	Balance between potency and pharmacokinetics [24]

Abbreviations: BCMA, B-cell maturation antigen; IgG1, immunoglobulin G1; FcγRIIIa, Fc gamma receptor IIIa; ADCC, antibody-dependent cellular cytotoxicity; MMAF, monomethyl auristatin F; cys-mcMMAF, cysteine maleimidocaproyl monomethyl auristatin F; DAR, drug-to-antibody ratio.

3.1. Antibody Structure

The antibody component, J6M0, is an IgG1 humanized from the murine clone 118G03. It binds cell-surface BCMA on MM cells and inhibits the interaction between BCMA and its ligands [24]. Afucosylation of the Fc region — that is, the absence of the core fucose on the N-glycan — markedly increases binding affinity for FcγRIIIa (CD16a) [27] and enhances natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC).

3.2. Linker Technology

Belantamab mafodotin contains a protease-resistant, non-cleavable maleimidocaproyl linker. Following cellular uptake, lysosomal proteolysis of the antibody component generates cys-mcMMAF, in which the payload remains attached to the linker and a cysteine residue [25,28]. This processing is not restricted to BCMA-positive tumor cells; cys-mcMMAF formation has also been demonstrated following BCMA-independent uptake by corneal epithelial cells [29]. This design has three principal consequences. First, premature payload release in the systemic circulation is minimal. Second, the low membrane permeability of cys-mcMMAF limits its diffusion into neighboring cells and therefore limits payload-mediated bystander killing. This should be distinguished from direct ADC targeting of cells with low BCMA expression, which depends on accessible surface antigen and subsequent intracellular processing. Third, the same property may predispose to accumulation of the catabolite, and hence to toxicity, in off-target cells that take up the ADC through non-specific routes — for example, the corneal epithelium [29,30].

3.3. MMAF Payload

MMAF is a synthetic auristatin derivative of dolastatin 10. The charged phenylalanine at its C-terminus renders it poorly membrane-permeable and limits its cytotoxic potency in free form; when delivered intracellularly by an antibody, however, it is highly cytotoxic [28]. By disrupting the microtubule network, it causes G2/M cell-cycle arrest and caspase-3-dependent apoptosis [24].

3.4. Intracellular Trafficking

The intracellular route of the ADC comprises the following steps. The ADC binds BCMA at the cell surface, and the ADC–BCMA complex is rapidly internalized [24]. Receptor-mediated

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endocytosis delivers it from the early endosome to the lysosome. Within the lysosome, the antibody is proteolytically degraded and cys-mcMMAF is released. In the cytosol, this catabolite disrupts microtubule dynamics.

A different picture applies to cells that do not express BCMA. In BCMA-negative primary human corneal epithelial cells and renal proximal tubule cells, the ADC undergoes antigen-independent uptake, colocalizes with lysosomes, and generates cys-mcMMAF, with uptake and cytotoxicity being more pronounced in corneal cells [29]. Macropinocytosis contributes to this uptake but has not been established as the sole entry pathway.

The endocytic route by which BCMA is internalized (clathrin-dependent or clathrin-independent) and the balance between surface-retained ADC available for ADCC and internalized ADC remain incompletely defined. Recent experimental evidence implicates the lysosomal transporter SLC46A3 in the export of auristatin catabolites, including cys-mcMMAF. However, functional evidence from an MMAF-containing ADC model was obtained with trastuzumab-mcMMAF, and the contribution of SLC46A3 to belantamab mafodotin activity in myeloma cells and clinical outcomes remains to be established [31].

4. Molecular Mechanisms of Action

Belantamab mafodotin targets the MM cell not through a single mechanism but through several complementary ones: direct cytotoxicity, ADCC, antibody-dependent cellular phagocytosis (ADCP), immunogenic cell death (ICD) and effects on the tumor microenvironment. The level of evidence for each mechanism is summarized in Table 2, and the mechanisms are depicted in Figure 2.

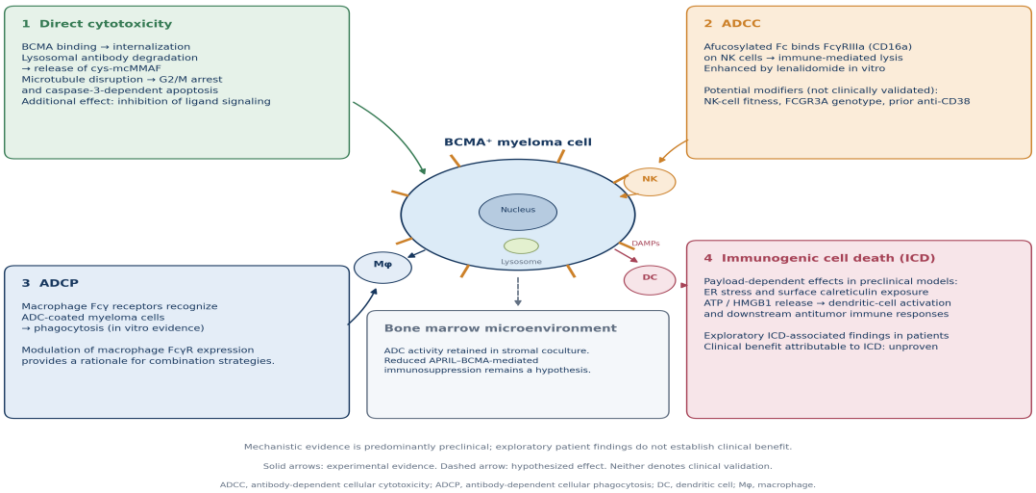

Figure 2. Mechanisms of action of belantamab mafodotin. (1) Direct cytotoxicity through BCMA-mediated internalization, lysosomal release of cys-mcMMAF and microtubule disruption; (2) NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) via the afucosylated Fc; (3) antibody-dependent cellular phagocytosis (ADCP) by macrophages; and (4) payload-dependent immunogenic cell death (ICD), with DAMP release and activation of antigen-presenting cells and downstream immune responses. Functional evidence for ICD derives primarily from preclinical models, with additional exploratory findings in patient samples; its contribution to clinical benefit remains unproven. Effects on the bone marrow microenvironment are summarized at the bottom. Solid arrows indicate direct experimental evidence, whereas dashed arrows indicate inferred or limited evidence; neither implies clinical validation. Mφ, macrophage; DC, dendritic cell; NK, natural killer cell; DAMPs, damage-associated molecular patterns; ER, endoplasmic reticulum [19,24,32,33,36].

Table 2. Mechanisms and level of evidence.

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Mechanism	Level of evidence	Key reference
Direct cytotoxicity	In vitro and in vivo (including patient cells)	[24]
ADCC	In vitro, autologous patient cells	[24]
ADCP	In vitro macrophage coculture	[24]
ICD	Functional preclinical evidence in cell and mouse models; exploratory ICD-associated findings in patient samples. Contribution to clinical benefit remains unproven.	[33,36]
Effects on the tumor microenvironment	In vitro coculture and in vivo; partly indirect evidence	[19,24,33]

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ICD, immunogenic cell death.

4.1. Direct Cytotoxicity

Binding to BCMA, internalization and release of cys-mcMMAF lead to G2/M arrest and caspase-3-dependent apoptosis. This effect has been demonstrated both in isolation and in coculture with bone marrow stromal cells or effector cells [24]. The ADC additionally inhibits BCMA signaling.

4.2. ADCC

The afucosylated Fc engages FcγRIIIa on NK cells with high avidity. Tai and colleagues showed that J6M0-mcMMAF increased effector-mediated lysis of both allogeneic and autologous patient MM cells relative to the antibody bearing an unmodified Fc, and that lenalidomide further enhanced both ADCC and apoptosis [24]. This finding provides the rationale for IMiD-containing combinations. NK cell number and fitness, FCGR3A polymorphisms and prior anti-CD38 therapy may all modulate ADCC, although these remain hypotheses at present.

4.3. ADCP

J6M0-mcMMAF recruits macrophages and increases the phagocytosis of MM cells by macrophages [24]. In the bone marrow niche, macrophage FcγR expression has been shown to determine resistance to antibody therapy, and cyclophosphamide can modulate this expression [32]. These observations provide a hypothesis for investigating whether cyclophosphamide can enhance macrophage-mediated responses to belantamab mafodotin. However, findings from other antibody-treatment models do not establish synergistic activity or clinical benefit for this specific combination [32].

4.4. Immunogenic Cell Death

Montes de Oca and colleagues reported that belantamab induces endoplasmic reticulum (ER) stress, surface calreticulin exposure and the release of high-mobility group box 1 (HMGB1) and adenosine triphosphate (ATP) in BCMA-expressing cells. In a BCMA-expressing EL4 lymphoma model, intratumoral immune cell infiltration and immune-mediated antitumor responses were observed in immunocompetent mice, with synergy demonstrated for an OX40 agonist. Notably, the unconjugated antibody did not trigger ICD; the effect is payload-dependent [33].

The detection of ICD-associated markers alone does not establish a functional antitumor immune response; experimental confirmation requires functional assessment, typically using vaccination assays in immunocompetent models [34,35]. For belantamab mafodotin, evidence of immune-mediated antitumor activity derives primarily from preclinical models [33]. Early translational findings consistent with ICD have also been reported in samples from patients with newly diagnosed MM within 24 hours of treatment [36]. These observations support the biological plausibility of this mechanism in humans, but its contribution to clinical response and durable disease control remains to be established.

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4.5. Effects on the Tumor Microenvironment

Preclinical studies suggest that belantamab mafodotin can influence the immune microenvironment through ICD-associated signals, including cell-surface exposure of calreticulin and release of ATP and HMGB1, together with changes in immune-cell recruitment and activation [33]. The extent to which these effects occur in the human bone marrow microenvironment and contribute to clinical benefit remains to be established. Belantamab mafodotin retained antimyeloma activity in bone marrow stromal coculture experiments [24]. However, retained activity does not exclude stromal protection: separate patient-derived coculture experiments linked mitochondrial transfer from stromal cells to reduced drug sensitivity [37]. These findings should be interpreted within their respective experimental conditions rather than as evidence that stromal interactions are uniformly permissive or protective. Ligand inhibition would be expected to reduce APRIL–BCMA-mediated immunosuppression [19,24]; direct data for belantamab in this regard are, however, limited.

5. Mechanisms of Resistance

Resistance should be distinguished as primary resistance, in which a clinical response is not achieved, or acquired resistance, in which disease progresses after an initial response. Reduced drug sensitivity in experimental models should not automatically be equated with either clinical phenotype. The mechanisms discussed below therefore need to be interpreted according to whether they are supported by patient observations, experimental models, or biological hypotheses. Establishing acquired resistance mechanisms requires longitudinal evidence rather than baseline associations alone.

5.1. Changes in BCMA Expression

Belantamab mafodotin requires accessible BCMA on the myeloma cell surface for target binding. Reduced expression or loss of BCMA may therefore contribute to resistance. Biallelic loss of TNFRSF17, the gene encoding BCMA, was documented in one patient who relapsed after belantamab mafodotin. In the clinical datasets analyzed, sBCMA was still measurable at progression in most patients. This finding suggests that complete loss of the target is unlikely to explain resistance in many cases. Detectable serum sBCMA does not, by itself, establish that every tumor cell retains sufficient surface BCMA for drug binding [24,38,39].

5.2. Soluble BCMA

γ-Secretase cleaves the extracellular domain of BCMA from the cell surface, generating sBCMA. Because sBCMA can bind belantamab mafodotin, high circulating concentrations could plausibly alter drug distribution or access to tumor cells. However, sBCMA also reflects disease burden, and an association between high sBCMA and poor response does not establish a drug-sink mechanism. In an exposure–response analysis of DREAMM-2, higher baseline sBCMA was associated with a lower probability of response and shorter progression-free survival [20,40].

γ-Secretase inhibition is being investigated as a way to reduce BCMA shedding and increase target availability on the cell surface. Experimental work with nirogacestat supports this biological effect. Clinical data on nirogacestat combined with belantamab mafodotin in DREAMM-5 have been reported as a conference abstract; they should not be interpreted as definitive evidence that the combination overcomes resistance in patients [41,42].

5.3. Intracellular Processing

Binding to BCMA is only the first step in belantamab mafodotin cytotoxicity. After internalization, the antibody component is degraded in lysosomes, yielding the active catabolite cys-mcMMAF. In an experimental study, SLC46A3 was shown to transport cys-mcMMAF; depletion of SLC46A3 also reduced the activity of a different MMAF-containing antibody–drug conjugate in the

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cells tested. Lysosomal transport could thus affect sensitivity to belantamab mafodotin. Whether SLC46A3 expression predicts outcomes in patients receiving this drug remains unknown [31,43].

Following lysosomal processing, the active catabolite cys-mcMMAF disrupts microtubule dynamics, contributing to cell-cycle arrest and cell death. Altered uptake or lysosomal processing of the conjugate, or a changed cellular response to its catabolite, could consequently reduce cytotoxicity. Clinical evidence remains limited on the relative importance of these steps in patients receiving belantamab mafodotin [24,31,43,44].

5.4. Drug Resistance Pathways

Even when BCMA binding and intracellular delivery of MMAF occur, the outcome also depends on how myeloma cells respond to cytotoxic injury. Alterations in cell-death pathways and protective signals from the bone marrow microenvironment are plausible contributors to resistance. Further studies are needed to determine whether they function as independent, measurable resistance mechanisms in patients treated with belantamab mafodotin [24,43].

Patient-derived cocultures provide a more specific example of stromal protection. Matula and colleagues observed increased transfer of mitochondria from autologous bone marrow stromal cells to myeloma cells with increasing belantamab mafodotin concentrations. This transfer was associated with reduced drug sensitivity, suggesting that metabolic support from neighboring cells may contribute to resistance even when the target is present. This remains an experimental observation rather than a demonstrated mechanism of clinical progression [37].

Efflux of cytotoxic payloads is another potential resistance pathway for antibody–drug conjugates, but its relevance depends on the particular payload. Follow-up cell-line experiments did not confirm MMAF as a substrate for the ATP-binding cassette (ABC) transporters examined. Increased ABCB1 expression should therefore not be presented as a clinically established mechanism of resistance to belantamab mafodotin [45].

5.5. Immune Escape

Belantamab mafodotin has effects beyond the direct cytotoxicity of MMAF. Its antibody component may also promote tumor-cell killing by immune effector cells. Preclinical models have demonstrated immunogenic cell death and immune-mediated antitumor responses after belantamab mafodotin treatment. Changes consistent with immunogenic cell death have also been reported in patient samples soon after treatment [24,33,36].

Changes in the immune microenvironment could therefore contribute to resistance. However, no specific immune-cell profile has been shown to predict response to belantamab mafodotin. In clinical study samples, T-cell and natural killer cell counts and the phenotypic markers examined did not support widespread systemic immune disruption after treatment; these measurements do not constitute direct testing of all cellular functions [39].

6. Ocular Toxicity and Its Clinical Management

Ocular toxicity is a central determinant of the feasibility of belantamab mafodotin treatment. A useful clinical framework must connect corneal injury with objective examination findings, visual function, and treatment exposure. These outcomes are related but are not interchangeable: microcyst-like epithelial changes (MECs), a reduction in best-corrected visual acuity (BCVA), and patient-reported blurred vision can occur with different timing and severity. Consequently, a symptom-only assessment can underestimate toxicity, whereas an isolated examination grade does not fully describe its impact on daily life [30,46].

6.1. Antigen-Independent Uptake and Intracellular Injury

Corneal epithelial uptake does not require membrane BCMA expression. Human cell experiments demonstrated intracellular generation of cys-mcMMAF, microtubule disruption, and

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apoptosis after exposure to an MMAF-containing BCMA antibody–drug conjugate. Inhibitors only partially reduced uptake, implicating multiple entry mechanisms. Macropinocytosis is therefore a contributing pathway, not an established exclusive route [29].

Human tissue provides complementary evidence. In a small corneal-characterization study, all six evaluable epithelial samples contained intracytoplasmic inclusions and five showed apoptosis. These observations support epithelial injury but do not establish every step of the proposed intracellular sequence in vivo. Detection of belantamab mafodotin in tear samples also demonstrates ocular exposure without proving that tear delivery is the dominant cause of toxicity [47].

6.2. Corneal Distribution and Unresolved Exposure Pathways

MECs are a descriptive clinical appearance, not evidence of fluid-filled epithelial cysts. DREAMM-2 documented peripheral, paracentral, and central involvement. Peripheral-to-central evolution is consistent with epithelial migration, while subsequent epithelial renewal offers a plausible explanation for improvement after treatment interruption. This spatial model remains an interpretation of clinical observations rather than direct tracking of drug-containing cells in humans [30].

Limbal delivery and tear-film exposure should be presented as candidate routes whose relative contributions remain uncertain. A separate translational study identified soluble BCMA in lacrimal fluid and proposed that BCMA–drug complexes might contribute to epithelial exposure. However, the small patient cohort and experimental findings do not establish tear BCMA as a validated predictor, a routine monitoring test, or a therapeutic target. This hypothesis must not be confused with proof of BCMA expression on corneal epithelial cells. Figure 3 separates experimental findings from proposed tissue-level pathways [47,48].

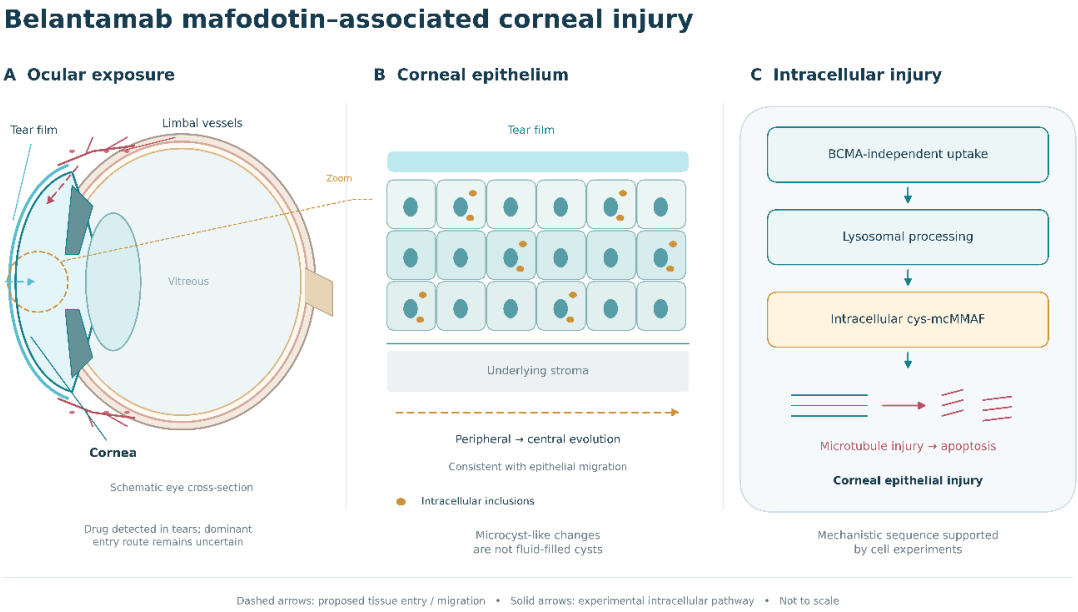

Figure 3. Evidence-based model of belantamab mafodotin-associated corneal injury. (A) Ocular exposure through the tear film and limbal vessels is proposed; drug detection in tears does not establish the dominant entry route. (B) Corneal epithelial inclusions and the proposed peripheral-to-central evolution of microcyst-like epithelial changes are illustrated. This distribution is consistent with epithelial migration but does not constitute direct tracking of drug-containing cells in humans. (C) Cell experiments support BCMA-independent uptake, lysosomal processing, intracellular cys-mcMMAF generation, microtubule injury, and apoptosis. Dashed arrows indicate proposed tissue-level relationships; solid arrows in panel C indicate experimental support, not proof of the complete sequence in patients. The soluble-BCMA hypothesis remains exploratory. Original schematic, not to scale [29,30,47,48].

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6.3. Clinical Burden and Interpretation of Recovery

The spectrum includes epithelial abnormalities, visual disturbance, and occasionally ulceration. A UK retrospective series reported keratopathy in 15/16 patients and grade 4 epithelial defects in four; one ulcer was asymptomatic. This selected cohort cannot establish incidence for contemporary combinations, but illustrates that symptoms may underestimate disease [49].

Recovery should be defined explicitly: improvement to grade 1 or lower, return to baseline acuity, and complete disappearance of corneal abnormalities are different endpoints. Analyses of DREAMM-7 and DREAMM-8 found that acuity could recover earlier than corneal examination findings. Statements that toxicity is universally or rapidly reversible therefore overstate the evidence. Persistent events at a study cutoff also cannot automatically be interpreted as permanent injury [50].

Patient-reported outcomes add information beyond examination grading. DREAMM-8 reported severe or very severe blurred vision in 63/146 patients receiving belantamab mafodotin–pomalidomide–dexamethasone (BPd) versus 13/139 receiving pomalidomide–bortezomib–dexamethasone (PVd). These are patient-reported severity categories, not ophthalmic examination grades. Broad quality-of-life scores may obscure an important visual burden; reading, driving, mobility, and independence deserve specific assessment [46]. Table 3 summarizes the studies informing ocular assessment and management.

Table 3. Studies informing ocular toxicity management.

Study	Design and population	Main finding or contribution	Clinical use and limitation
Farooq et al. 2020 [30]	DREAMM-2 ocular characterization; 95 patients at 2.5 mg/kg.	MECs in 68/95 patients; mapped epithelial patterns and their relationship to visual findings.	Supports slit-lamp examination alongside acuity. Descriptive analysis; not a comparison of preventive therapies.
Lonial et al. 2021 [51]	DREAMM-2-derived clinical management guidance.	Combined corneal and acuity grading; dose modification and supportive eye care. Steroid prophylaxis lacked demonstrated benefit.	Foundational management paper. Historical dosing instructions must be checked against current regional labels.
Mateos et al. 2025 [50]	Post hoc analyses of DREAMM-7 and DREAMM-8; safety populations 242 BVd and 150 BPd.	Described ocular recovery and treatment delivery after dose delays, reductions, and longer intervals.	Supports exposure adaptation in practice. Not randomized evidence that all extended schedules maintain efficacy.
Terpos et al. 2025 [52]	International hematology–ophthalmology expert guidance.	Structured baseline assessment, communication, functional questioning, and later-cycle management.	Useful workflow proposals; expert recommendations are not equivalent to regulatory requirements or intervention-trial evidence.

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Study	Design and population	Main finding or contribution	Clinical use and limitation
Sunami et al. 2025 [53]	Japanese expert-panel recommendations.	Practical multidisciplinary approaches to recognizing, monitoring, and managing ocular events.	Provides operational guidance; local applicability and prescribing requirements must be checked.
Arazi et al. 2025 [54]	Retrospective clinical-practice cohort; 41 patients.	Keratopathy in 38/41; median onset 4.14 weeks. Examined clinician-selected dose changes and subsequent ocular findings.	Demonstrates interdisciplinary management. Confounding by severity limits comparisons of dose reduction with interruption.
Schimansky et al. 2026 [49]	Two UK tertiary centers; retrospective series of 16 patients.	Keratopathy in 15/16; four grade 4 epithelial defects. Substantial specialist follow-up requirements.	Highlights severe disease and service burden. Small selected cohort; topical interventions were not controlled.
Keye et al. 2023 [55]	Single-patient report of rigid gas-permeable lenses.	Improved visual function with specialist optical rehabilitation.	Hypothesis-generating rescue option; no evidence of prevention or permission to disregard dose-hold criteria.
Lee et al. 2025 [47]	Phase IIIb corneal-characterization study; nine enrolled, six evaluable tissue samples.	Intracellular inclusions in all six samples; apoptosis in five. Drug detected in five of seven tear samples.	Human evidence of epithelial injury; route of exposure remains incompletely established. Not a management trial.
Munawar et al. 2024 [48]	Translational study; tear samples from nine patients and seven healthy participants, with experimental work.	Proposed a role for lacrimal soluble BCMA and drug–BCMA complexes in epithelial exposure.	Exploratory mechanism and biomarker; no validated clinical threshold or proven preventive intervention. Read with the published erratum.
Newman et al. 2026 [29]	Human corneal epithelial cell experiments.	BCMA-independent uptake, intracellular catabolite formation, microtubule injury, and apoptosis; partial inhibition of uptake.	Supports mechanistic plausibility. Immunoglobulin protection was in vitro and cannot establish clinical prophylaxis.

Abbreviations: MECs, microcyst-like epithelial changes; BVd, belantamab mafodotin–bortezomib–dexamethasone; BPd, belantamab mafodotin–pomalidomide–dexamethasone. These selected publications provide a narrative evidence map, not an exhaustive systematic-review dataset.

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6.4. Baseline Assessment and Coordinated Monitoring

Before treatment, assessment should establish baseline acuity and corneal status, identify relevant ocular history and current treatments, and document functional limitations. The ophthalmic report should communicate corneal findings and change in BCVA separately, together with the most severe finding and the follow-up plan. Hematology and eye-care teams need a reliable route for exchanging this information before dosing decisions. Expert guidance supports this coordinated approach, but its suggested workflow must be reconciled with the applicable product information [52,53].

United States (US) and European Union (EU) examination schedules differ (Table 4). Symptom questionnaires cannot replace examinations required by the applicable label [56,57].

New pain, marked redness, photophobia, or sudden visual deterioration warrants prompt ophthalmic assessment rather than waiting for the next planned infusion visit. Epithelial defects require evaluation for infection and other ocular pathology; they should not simply be attributed to uncomplicated drug-related MECs. The need for additional visits and transport assistance should be discussed when planning treatment, particularly for patients with limited visual reserve or difficulty accessing specialist care [49,53].

6.5. Grading and Treatment Modification

Dose decisions require an objective assessment of corneal findings and BCVA, using the applicable grading framework. Historical keratopathy and visual acuity (KVA)-based trial algorithms, Common Terminology Criteria for Adverse Events (CTCAE) symptom grades, and current regional prescribing tables must not be treated as identical. In particular, the US and EU thresholds for a grade 2 versus grade 3 acuity decline differ [51,56,57].

Treatment modification must follow the regional and regimen-specific rules summarized in Table 4 and Figure 4; symptomatic improvement alone is insufficient to authorize restarting [56,57].

Table 4. Regional prescribing differences relevant to ocular care.

Decision	United States BVd	European Union BVd or BPd
Examination schedule	Baseline and before every dose; additional assessment for new or worsening symptoms.	Before the first four doses; thereafter as clinically indicated.
Acuity component of grading	Grade 2: two-line decline. Grade 3: ≥3 lines. Both retain acuity no worse than 20/200. Any MECs are at least grade 2.	Grade 2: two- or three-line decline. Grade 3: >3 lines. Both retain acuity no worse than 20/200.
Grade 2 or 3	Hold until BOTH cornea and BCVA are ≤grade 1. Resume at 1.9 mg/kg every 3 weeks; recurrence: 1.9 mg/kg every 8 weeks.	Hold until BOTH are ≤grade 1. BVd: 1.9 mg/kg every 3 weeks. BPd: 1.9 mg/kg every 8 weeks; if identified before cycle 2, 1.9 mg/kg every 4 weeks.
Grade 4	Consider permanent discontinuation; if resuming after recovery, use the label's reduced level. Recurrent grade 4: permanently discontinue.	After recovery, BVd: 1.9 mg/kg every 3 weeks; BPd: 1.4 mg/kg every 8 weeks, if applicable. Consider discontinuation for worsening unresponsive symptoms.
Ocular dose re-escalation	Do not re-escalate after ocular dose reduction.	Do not re-escalate after ocular dose reduction.

Grade 1 generally permits continuation. Grade 4 includes an epithelial defect/ulcer or acuity worse than 20/200. "Both" refers to the corneal examination and BCVA criteria. Treatment rules are not

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interchangeable across jurisdictions. Abbreviations: BCVA, best-corrected visual acuity; MECs, microcyst-like epithelial changes; BVd, belantamab mafodotin–bortezomib–dexamethasone; BPd, belantamab mafodotin–pomalidomide–dexamethasone; FDA, US Food and Drug Administration; EMA, European Medicines Agency. Source versions: FDA October 2025 label and EMA product information accessed 10 November 2026 [56,57].

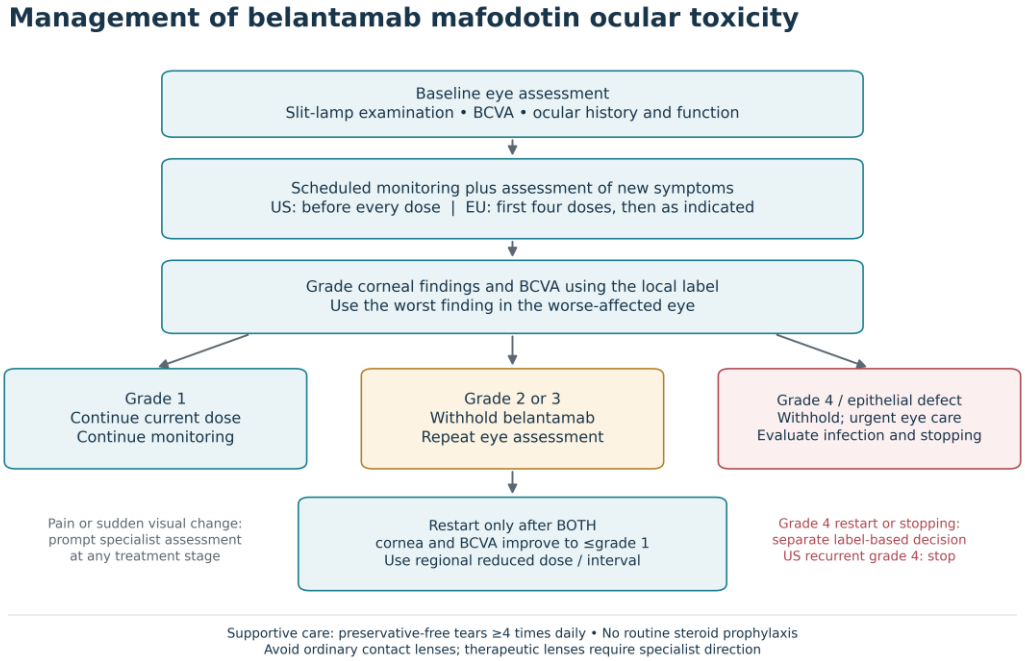

Figure 4. Clinical decision framework for ocular toxicity during belantamab mafodotin treatment. Examination findings, acuity, and symptoms inform coordinated decisions; grading thresholds and restart regimens must follow the applicable product information (Table 4). Severe events require specialist assessment and a separate continuation decision. Supportive care does not replace treatment modification. This overview does not reproduce all label conditions [51–53,56,57].

Post hoc DREAMM-7/8 analyses suggest that responses can persist or deepen during toxicity-related delays. These findings support exposure adaptation, but do not prove efficacy preservation with any extended interval. Dose-modification strategies were not randomized, and patients who remain on treatment represent a selected population. Myeloma control and ocular recovery require joint reassessment [50].

6.6. Supportive Care and Management of Epithelial Defects

Preservative-free artificial tears, used at least four times daily as advised in the US and EU product information [56,57], are a routine supportive measure, although relief of dryness should not be equated with prevention of intracellular payload injury. Prophylactic topical corticosteroids did not demonstrate a preventive benefit in the DREAMM-2 ocular substudy and should not be presented as standard protection against keratopathy. This does not exclude specialist-directed corticosteroid treatment for a separate inflammatory indication [51].

For epithelial defects, the ophthalmologist should direct treatment according to the lesion and the possibility of infection. The UK series describes intensive lubrication, antimicrobial treatment, and treatment delays in affected patients; its uncontrolled design cannot establish the comparative efficacy of any topical regimen. Routine prophylactic antibiotics for all treated patients are not justified by such observations [49].

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A single report of rigid gas-permeable lenses suggests that optical rehabilitation can improve vision in selected circumstances. It does not establish epithelial protection or justify overriding dose-hold criteria. Specialist therapeutic lens use must be distinguished from ordinary contact-lens wear during treatment. Cooling, additional topical agents, and other proposed protective approaches require prospective evaluation before being described as proven preventive interventions [53,55].

6.7. Evidence for Management and Its Limitations

Table 3 distinguishes clinical characterization, management guidance, observational practice, and mechanistic work. The evidence is strongest for identifying toxicity and adapting treatment exposure; evidence for pharmacological prevention remains limited. The 41-patient retrospective study by Arazi and colleagues is particularly relevant to interdisciplinary care: keratopathy occurred in 38 patients, and management varied with its severity. However, comparisons between dose reduction and treatment interruption are vulnerable to confounding by indication, because clinicians preferentially interrupt treatment in more severe cases. Such data cannot establish that interruption itself worsens toxicity [54].

Expert panels provide useful approaches to communication, functional assessment, and monitoring logistics. They are not randomized tests of a management strategy. Recommendations permitting less frequent examinations or broader interval extension should be identified as expert proposals and applied only within the relevant regulatory framework. Future studies should compare prespecified schedules and report corneal grade, acuity, symptoms, treatment exposure, and discontinuation separately [52,53].

6.8. Translational Priorities

Mechanistic prevention should be judged by whether it protects the cornea without compromising antimyeloma activity. Human immunoglobulin reduced uptake and apoptosis in cell experiments, but this is not evidence that topical immunoglobulin or systemic intravenous immunoglobulin prevents clinical keratopathy. Likewise, tear soluble BCMA remains an exploratory biomarker rather than a basis for individual dose selection [29,48].

Prospective studies should prioritize time to meaningful visual recovery, recurrent events, persistent epithelial defects, and the practical burden of eye-care visits. A clinically useful preventive strategy would need to improve these outcomes while maintaining disease control. The proposed framework in Figure 4 therefore links examination findings, patient function, and treatment decisions without assuming that supportive drops can replace exposure modification.

7. Biomarkers of Response and Resistance

7.1. Surface Antigen and Target Loss

None of the candidate biomarkers discussed here has been clinically validated to guide pretreatment patient selection for belantamab mafodotin. Surface BCMA is a biologically compelling candidate: in cultures of patient-derived myeloma cells, low BCMA expression was associated with resistance to belantamab mafodotin. This experimental association does not provide a clinically useful cutoff. A measurement from one bone marrow sample may also fail to capture heterogeneity across tumor cells [37,39]. Demonstrating TNFRSF17 loss at relapse may explain resistance in an individual patient, but this mechanism should not be generalized to all cases of progression [38,39].

7.2. Serum sBCMA and Drug Exposure

In the DREAMM-2 analysis, baseline serum sBCMA was associated with response probability and progression-free survival; beta-2-microglobulin was also included in the progression-free survival model. Because these measures are intertwined with disease burden and drug exposure, no sBCMA threshold has been established for choosing treatment on its own [40].

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The exposure–response findings require a distinction between an association with outcome and a marker of treatment-specific benefit. In DREAMM-2, exposure was associated with efficacy in univariate analyses, but was not retained in the final response or progression-free survival models after disease-burden variables were considered. Baseline sBCMA should therefore be interpreted alongside disease burden and pharmacokinetics, rather than as an isolated measure of cellular resistance. These models do not establish that patients with a particular sBCMA level benefit more from belantamab than from another treatment [40].

7.3. Intracellular Processing and Exploratory Biomarkers

Other areas of biomarker research include lysosomal processing, intracellular transport of MMAF, and the effects of bone marrow stromal cells. In patient-derived myeloma–stromal cocultures, mitochondrial transfer from stromal cells to myeloma cells was associated with resistance to belantamab mafodotin. These experimental findings are not ready for use in treatment selection. Future clinical studies should assess them alongside established measures of myeloma response [31,37,43].

Biomarkers of toxicity should also be distinguished from biomarkers of tumor response. Higher ADC exposure was associated with more frequent corneal events in DREAMM-2, whereas lacrimal sBCMA remains an exploratory candidate. A useful ocular biomarker would need prospective validation against ophthalmic findings and visual function, rather than confirmation of antigen or drug in tears alone. Future studies should specify sampling time, assay methods and clinical endpoints before defining thresholds for treatment selection or toxicity prediction [30,40,47,48]. Candidate biomarkers of response, resistance, and ocular toxicity, together with the supporting evidence and limitations of their clinical application, are summarized in Table 5.

Table 5. Candidate biomarkers of response, resistance and ocular toxicity.

Candidate marker	Relevant finding	Clinical use
Cell-surface BCMA	Low expression was associated with reduced sensitivity in patient-derived cell cultures [37].	No clinical cutoff has been validated.
Baseline serum sBCMA	Higher levels were associated with a lower response probability and shorter progression-free survival in a DREAMM-2 analysis [40].	No threshold for treatment selection on its own.
TNFRSF17 loss	Biallelic loss was reported in one patient after belantamab mafodotin [38]; it was not found to be a common mechanism [39].	May be investigated in selected cases of relapse.
SLC46A3	An experimental role in cys-mcMMAF transport was demonstrated [31].	Predictive value in belantamab-treated patients is unknown.
Stromal mitochondrial transfer	Associated with resistance in patient-derived coculture experiments [37].	Experimental finding; not a clinical test.
Lacrimal sBCMA	Detected in tear fluid; sBCMA-bound ADC uptake was investigated in corneal epithelial cultures [48].	Exploratory candidate; predictive value for keratopathy is unconfirmed.

Abbreviations: BCMA, B-cell maturation antigen; sBCMA, soluble BCMA; ADC, antibody–drug conjugate; TNFRSF17, TNF receptor superfamily member 17 (the BCMA gene); SLC46A3, solute carrier family 46 member 3; cys-mcMMAF, cysteine maleimidocaproyl monomethyl auristatin F.

8. Clinical Development and Recent Phase III Evidence

8.1. DREAMM-7

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Belantamab mafodotin is an antibody–drug conjugate targeting BCMA. DREAMM-7 is an open-label, randomized phase III trial comparing belantamab mafodotin plus bortezomib and dexamethasone (BVd) with daratumumab plus bortezomib and dexamethasone (DVd) in patients with relapsed/refractory multiple myeloma (RRMM) who had received at least one prior line of therapy. A total of 494 patients were randomized in a 1:1 ratio (BVd, n=243; DVd, n=251). The primary endpoint was progression-free survival (PFS) [9,58,59]. Patients who were refractory or intolerant to daratumumab or bortezomib, or who had previously received BCMA-directed therapy, were excluded [9,59]. These eligibility criteria limit the direct applicability of the findings to patients with anti-CD38-refractory disease or prior BCMA-directed treatment, populations that are increasingly relevant as these therapies move into earlier treatment lines.

At a median follow-up of 28.2 months, median PFS was 36.6 months in the BVd group and 13.4 months in the DVd group (hazard ratio [HR] for disease progression or death, 0.41; 95% confidence interval [CI], 0.31–0.53; P<0.001). Prespecified subgroup analyses generally favored BVd, including in patients with lenalidomide-refractory disease and those with high-risk cytogenetic features. These subgroup findings should be interpreted in the context of their sample sizes and confidence intervals rather than as independent demonstrations of superiority within every subgroup [9]. The overall response rate was 82.7% in the BVd group and 71.3% in the DVd group. The rate of complete response or better was 34.6% with BVd and 17.1% with DVd [9]. The median duration of response was 35.6 months in the BVd group and 17.8 months in the DVd group [9,59].

At the first interim analysis, the estimated 18-month overall survival (OS) rates were 84% with BVd and 73% with DVd [9]. At the second interim analysis, with a median follow-up of 39.4 months, BVd demonstrated a statistically significant OS benefit (HR for death, 0.58; 95% CI, 0.43–0.79; P=0.0002). Median OS had not been reached in either group [58]. At the primary analysis, the proportion of patients achieving both a complete response or better and measurable residual disease (MRD) negativity, assessed by next-generation sequencing at a sensitivity threshold of 10^{-5}, was 24.7% (60/243) in the BVd group and 9.6% (24/251) in the DVd group. These percentages were calculated using the intention-to-treat population as the denominator, rather than only patients achieving a complete response or better. MRD negativity in conjunction with a complete response or better was a prespecified key secondary endpoint [9,59].

Ocular events represent the major toxicity associated with belantamab mafodotin. According to the US Food and Drug Administration (FDA) assessment of DREAMM-7 data, ocular toxicity occurred in 92% of patients in the belantamab group, was grade 3 or 4 in 77%, and required dose modification in 83% [60]. In the initial analysis, treatment discontinuation due to ocular events was reported in 9% of patients [9]. Among grade ≥3 hematologic and infectious adverse events, thrombocytopenia occurred more frequently with BVd than with DVd (55% vs 35%). Neutropenia (12% vs 6%) and pneumonia (12% vs 4%) were also more frequently reported in the BVd group [9].

8.2. DREAMM-8

DREAMM-8 is an open-label, randomized phase III trial comparing belantamab mafodotin plus pomalidomide and dexamethasone (BPd) with bortezomib plus pomalidomide and dexamethasone (PVd) in patients with RRMM who had received at least one prior line of therapy, including lenalidomide. Patients were required to have had no prior exposure to anti-BCMA therapy or pomalidomide and not to be refractory or intolerant to bortezomib. A total of 302 patients were randomized 1:1 (BPd, n=155; PVd, n=147). In the BPd group, belantamab mafodotin was administered at 2.5 mg/kg during the first cycle and at 1.9 mg/kg every four weeks from the second cycle onward. Pomalidomide was administered orally at 4 mg daily on days 1–21, and dexamethasone at 40 mg on days 1, 8, 15, and 22 of each 28-day cycle. The dexamethasone dose could be reduced to 20 mg on the scheduled dosing days at the investigator's discretion for patients older than 75 years, those with comorbidities, or those unable to tolerate 40 mg [10,61]. Overall, 53% of patients had received one prior line of therapy, while prior exposure to anti-CD38 antibodies was reported in 25% of patients

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in the BPd group and 29% in the PVd group. The primary endpoint was PFS, as assessed by an independent review committee [10].

At a median follow-up of 21.8 months, median PFS was not reached in the BPd group and was 12.7 months in the PVd group. The HR for disease progression or death was 0.52 (95% CI, 0.37–0.73; P<0.001), favoring BPd [10]. The 12-month PFS rates were 71% versus 51%, and the overall response rates were 77% versus 72%, respectively. The rate of complete response or better was 40% with BPd and 16% with PVd. At this interim analysis, the HR for death was 0.77 (95% CI, 0.53–1.14). Although the point estimate favored BPd, an OS benefit was not established, and follow-up was ongoing [10].

In the updated analysis presented at ASH 2025, with a data cutoff of July 7, 2025, and a median follow-up of 35.8 months, median PFS was 32.6 months with BPd and 12.5 months with PVd (HR, 0.49; 95% CI, 0.36–0.67) [62]. The 24-month PFS rates were 55% and 31%, respectively. Median PFS2, defined as the time from randomization to disease progression after initiation of subsequent antimyeloma therapy or death from any cause, whichever occurred first, was 47.1 months with BPd and 21.7 months with PVd (HR, 0.52; 95% CI, 0.38–0.70) [62,63]. Overall response rates were 76% versus 72%, while the rates of complete response or better were 43% versus 17%. Median duration of response was not reached in the BPd group and was 16.4 months in the PVd group. The 24-month duration-of-response rates were 65% and 40%, respectively [62].

At a median follow-up of 35.8 months, a complete response or better together with MRD negativity was achieved by 28% (43/155) of patients in the BPd group and 6% (9/147) in the PVd group. A complete response or better with MRD negativity sustained for at least 12 months was reported in 15% (24/155) and 3% (4/147), respectively. All percentages were calculated using the intention-to-treat population as the denominator [62].

In a subgroup analysis reported at ASCO 2025, patients with at least one prespecified high-risk cytogenetic abnormality had a median PFS of 21.1 months with BPd and 9.2 months with PVd (HR, 0.58; 95% CI, 0.36–0.95). The rates of complete response or better were 43% and 15%, respectively [64]. These findings support activity in this subgroup but do not establish that BPd overcomes the adverse prognosis associated with high-risk cytogenetics or provides a greater relative benefit than in standard-risk disease.

In the ASH 2025 analysis, any adverse event was reported in more than 99% of patients in the BPd group and in 97% of those in the PVd group. Grade 3–4 adverse events occurred in 91% versus 74% of patients. Adverse events led to permanent discontinuation of at least one treatment component in 22% (33/150) of patients receiving BPd and 14% (21/145) receiving PVd [62]. These percentages do not specifically represent discontinuation of belantamab mafodotin or cessation of the entire regimen. Adverse events led to dose reductions and dose interruptions or delays in 63% and 91% of patients receiving BPd, compared with 61% and 76% receiving PVd, respectively. The updated safety profile was reported to be largely consistent with that observed in the primary analysis [62]. In the primary analysis, grade ≥3 ocular adverse events occurred in 43% of patients receiving BPd (grade 3, 42%; grade 4, 1%). Grade ≥3 neutropenia (57% vs 39%), thrombocytopenia (38% vs 29%), and pneumonia (17% vs 8%) were more frequent in the BPd group [10]. The neutropenia and thrombocytopenia summaries use grouped event categories incorporating related clinical and blood-count terms; these should be distinguished from rates for individual Medical Dictionary for Regulatory Activities (MedDRA) preferred terms or laboratory abnormalities alone [63]. The 43% rate of grade ≥3 ocular adverse events should not be directly compared with the grade 3–4 ocular toxicity rate reported in the FDA assessment of DREAMM-7 without harmonizing event definitions, grading methods, assessment schedules, and follow-up periods. Differences in belantamab dosing and treatment exposure further complicate cross-trial comparisons. These rates alone therefore do not establish that BPd has a more favorable ocular safety profile than BVd.

In the patient-reported outcome analysis, overall health-related quality of life remained broadly stable in both treatment groups. However, blurred vision was reported as severe or very severe by 43% (63/146) of evaluable patients receiving BPd and 9% (13/139) receiving PVd. These patient-reported symptom categories should be distinguished from clinician-graded ocular adverse events.

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Thus, preservation of overall quality-of-life scores should be interpreted alongside the substantial visual symptom burden experienced by some patients [46]. The pivotal phase III trials informing the clinical repositioning of belantamab mafodotin are summarized in Table 6.

Table 6. Selected efficacy outcomes from pivotal phase III trials of belantamab mafodotin.

Trial	Population	Comparison	Median PFS, months; HR (95% CI)	OS interpretation
DREAMM-3 [65]	RRMM; ≥2 prior lines; N=325	Belantamab monotherapy vs Pd	Final analysis: 11.2 vs 7.0; 0.87 (0.64–1.18)	No OS advantage established; HR 0.98 (0.73–1.30)
DREAMM-7 [9,58]	RRMM; ≥1 prior line; N=494	BVd vs DVd	Primary analysis: 36.6 vs 13.4; 0.41 (0.31–0.53)	Significant benefit at the second interim analysis; HR 0.58 (0.43–0.79)
DREAMM-8 [10,62]	RRMM; ≥1 prior line including lenalidomide; N=302	BPd vs PVd	Updated analysis: 32.6 vs 12.5; 0.49 (0.36–0.67)	OS follow-up ongoing at the cited updated analysis

Abbreviations: RRMM, relapsed/refractory multiple myeloma; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; Pd, pomalidomide–dexamethasone; BVd, belantamab mafodotin–bortezomib–dexamethasone; DVd, daratumumab–bortezomib–dexamethasone; BPd, belantamab mafodotin–pomalidomide–dexamethasone; PVd, pomalidomide–bortezomib–dexamethasone. Outcomes are reported from the analyses specified above; follow-up and eligibility criteria differ between trials, precluding direct cross-trial efficacy comparisons. DREAMM-3 did not meet its primary PFS superiority endpoint; its final analysis was descriptive.

9. Combination Strategies and Clinical Repositioning

In DREAMM-3, single-agent belantamab mafodotin did not demonstrate superiority over pomalidomide plus dexamethasone for the primary PFS endpoint. In the final analysis published in October 2026, median PFS was 11.2 versus 7.0 months (HR, 0.87; 95% CI, 0.64–1.18), and median OS was 24.0 versus 22.9 months (HR, 0.98; 95% CI, 0.73–1.30). Although median duration of response was longer with belantamab mafodotin (25.3 versus 9.9 months), these findings did not establish a PFS or OS advantage over the comparator [65]. The results highlight the distinction between durable responses in responding patients and a survival benefit across the randomized population.

In combination with bortezomib and dexamethasone (DREAMM-7) or pomalidomide and dexamethasone (DREAMM-8), belantamab mafodotin demonstrated significant improvements in PFS, leading to updates in regulatory approvals [9,10,60,66]. On October 23, 2025, the FDA approved belantamab mafodotin in combination with bortezomib and dexamethasone for patients who had received at least two prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent [60]. In the EU, the European Commission granted marketing authorization on July 23, 2025, for belantamab mafodotin in combination with bortezomib and dexamethasone after at least one prior therapy, and in combination with pomalidomide and dexamethasone after at least one prior therapy including lenalidomide [66]. Thus, the approved combinations and prior-treatment requirements differ between the EU and the US.

Belantamab mafodotin has been investigated in clinical trials in combination with pomalidomide, lenalidomide, bortezomib, pembrolizumab, and the γ-secretase inhibitor nirogacestat (DREAMM-4, -5, -6, -7, -8, and -9). Preliminary clinical activity has been reported with the nirogacestat combination in a small conference-reported study [42]. No drug–drug interaction between belantamab and lenalidomide was identified, and no new safety signals were observed when belantamab was combined with bortezomib, lenalidomide, and dexamethasone (VRd) [67]. Another recent review considers the combination of belantamab with standard antimyeloma

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backbones (GEM-BelaVRd, DREAMM-10) and novel agents such as γ-secretase inhibitors among potential future strategies [68]. A phase Ib/II study of belantamab mafodotin with elotuzumab has reported preliminary safety and activity findings; mature efficacy results are needed to define its clinical role [69].

The final analysis of DREAMM-9, reported as a conference abstract from a phase I study, evaluated belantamab mafodotin plus bortezomib, lenalidomide, and dexamethasone (BVRd) in 118 transplant-ineligible patients with newly diagnosed multiple myeloma. The study included multiple cohorts evaluating doses ranging from 1.0 to 1.9 mg/kg and dosing intervals ranging from three to twelve weeks, with high response rates reported across all cohorts. Higher dose intensity during induction was associated with deeper responses, whereas longer dosing intervals were associated with improved tolerability and maintained responses in the observed cohorts. These nonrandomized comparisons do not establish equivalent efficacy across schedules [70]. The DREAMM-10 phase III protocol uses belantamab mafodotin at 1.9 mg/kg every eight weeks for 24 weeks, followed by every twelve weeks [71].

DREAMM-10 is comparing belantamab mafodotin plus lenalidomide and dexamethasone (BRd) with daratumumab plus lenalidomide and dexamethasone (DRd) in transplant-ineligible patients with newly diagnosed multiple myeloma [71]. PrE1005 is comparing belantamab mafodotin plus VRd with daratumumab plus VRd in newly diagnosed patients who are ineligible for or defer transplantation [72]. These studies will help define the role of belantamab-containing regimens in newly diagnosed disease.

A systematic review and network meta-analysis assessed the relative efficacy of belantamab mafodotin plus bortezomib and dexamethasone in early relapsed multiple myeloma [73]. Its overall survival findings should be interpreted as indirect comparative estimates rather than evidence of superiority over all alternative regimens. Differences between trials in prior treatment exposure, refractory status, follow-up duration, and subsequent therapies may affect the comparability of outcomes. These findings can contextualize the randomized evidence but do not establish a definitive treatment hierarchy.

Belantamab-associated ocular toxicity is thought to involve BCMA-independent uptake of the ADC by corneal epithelial cells, followed by intracellular formation of cys-mcMMAF, microtubule disruption, and epithelial injury [29]. Close ophthalmologic monitoring is required, and toxicity may be partially mitigated through dose reduction or extension of the dosing interval. Further data are needed to optimize dosing strategies, as discussed in recent practical guidance [74]. In DREAMM-9, longer dosing intervals were associated with fewer ocular events [70]. The phase II DREAMM-15 study is evaluating extended dosing intervals and combinations with standard-of-care therapies with the aim of reducing ocular toxicity [75].

Evidence on BCMA-directed treatment sequencing should distinguish outcomes of subsequent therapies after belantamab mafodotin from outcomes of belantamab after prior BCMA-directed therapy. In a multicenter retrospective series of 23 patients receiving BCMA-directed CAR-T-cell therapy or bispecific antibodies after belantamab, the overall response rate was 65% (79% with CAR-T-cell therapy and 44% with bispecific antibodies); median PFS was 7 and 5 months, respectively [76]. A separate single-center retrospective analysis reported no adverse association between prior anti-BCMA ADC exposure and long-term outcomes with subsequent BCMA-directed bispecific antibodies [77]. These findings support the feasibility of subsequent BCMA targeting but do not establish an optimal treatment sequence.

The reverse sequence was evaluated in a real-world series of 94 patients treated with belantamab mafodotin, in which the overall response rate was 43%. Among patients previously exposed to BCMA-directed therapy, the response rate was 29% and median PFS was 2 months [78]. These results describe belantamab activity after prior BCMA targeting and should not be interpreted as evidence about the efficacy of CAR-T-cell therapy or bispecific antibodies administered after belantamab. Differences in patient selection, prior treatment burden, and disease characteristics limit comparisons across these retrospective cohorts.

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According to expert opinion, CAR-T-cell therapy tends to be less effective following prior exposure to bispecific antibodies or antibody–drug conjugates. Conversely, bispecific antibodies administered after CAR-T-cell therapy may also perform less effectively than in BCMA-naïve patients [79]. Some experts favor administering CAR-T-cell therapy before belantamab in eligible patients; however, this approach represents an expert preference rather than a prospectively validated sequencing strategy [79,80]. For patients who are not candidates for CAR-T-cell therapy, the suitability of a belantamab-containing regimen should be assessed individually, considering functional status, ocular health, the feasibility of ophthalmologic monitoring, and the toxicity profile of the combination partners, rather than age or frailty alone. However, currently available real-world evidence is largely derived from heavily pretreated populations and may not fully reflect outcomes in patients treated at earlier lines of therapy [80].

10. Future Perspectives and Conclusions

The randomized DREAMM-7 and DREAMM-8 trials establish the efficacy of BVd and BPd, respectively, in patients resembling their enrolled populations [9,10]. BVd improved both PFS and OS compared with DVd, whereas an OS benefit for BPd has not been established at the cited updated analysis [58,62]. These findings should be distinguished from DREAMM-3, in which monotherapy did not meet the primary PFS superiority endpoint [65]. Clinical selection should account for previous treatment exposure and refractoriness, ocular health, monitoring feasibility, the tolerability of the combination partners, and locally approved indications [56,57].

Dose and schedule optimization remain priorities because ocular toxicity frequently requires treatment modification. DREAMM-9 provides exploratory evidence for dose selection in newly diagnosed disease, while DREAMM-10 and PrE1005 will assess the efficacy of their respective regimens in randomized phase III trials [70–72]. DREAMM-15 is evaluating extended dosing schedules in relapsed/refractory disease [75]. Preliminary findings with elotuzumab and nirogacestat support further evaluation but do not establish these combinations as routine treatment options [42,69].

Evidence on BCMA-directed treatment sequencing remains heterogeneous and insufficient to establish an optimal sequence. Responses to CAR-T-cell therapies and bispecific antibodies have been reported after belantamab, while separate cohorts describe belantamab activity after previous BCMA-directed therapy [76–78]. These studies address different sequences and are subject to selection bias and differences in disease burden. Suggestions to prioritize CAR-T-cell therapy in eligible patients remain based on expert opinion rather than prospective comparisons [79,80]. Ineligibility for CAR-T-cell therapy, older age, or frailty alone does not establish suitability for a belantamab-containing regimen.

Future translational studies should determine which biological features predict benefit from belantamab mafodotin and which merely reflect disease burden. Priorities include longitudinal assessment of cell-surface and soluble BCMA, intracellular ADC processing, payload sensitivity, and immune effector function. Paired pretreatment and progression samples could help distinguish changes in target availability from resistance downstream of ADC internalization. These studies should be integrated with clinical outcomes and ocular toxicity assessments to evaluate whether candidate biomarkers can inform patient selection or dosing.

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